INTERGROUP TRIAL 9741, reported in this issue of the Journal of Clinical Oncology by Citron et al., was launched in 1997 to test two novel concepts based on mathematical models of tumor cell growth kinetics that were articulated by Norton 15 years ago. The first concept implies that dose densification of chemotherapy—delivering chemotherapy at reduced intervals—will maximize the chances of eradicating the tumor. The second concept addresses heterogeneous drug sensitivity through the use of sequential dose-dense, non–cross-resistant single agents or regimens. It is truly fascinating to witness this elegant mathematical model materializing, at least in part, in the positive results of a randomized clinical trial.

The credit for using mathematics as a way to better understand how chemotherapy might affect the kinetics of mammary tumor cell growth is given to Skipper, who in 1971 introduced the important concept of log cell kill, in which a given dose of cytotoxic chemotherapy kills a constant fraction of the tumor. This theory, derived from murine experiments, was revisited by Norton and Simon and later refined by Norton to match the data generated by clinical trials of adjuvant chemotherapy conducted in the last two decades. The growth curves that best fit these data had a sigmoid (Gompertzian) shape, and simulations of chemotherapy effects predicted that the simple manipulation of compressing the conventional schedule of drug administration would achieve considerably greater efficacy by minimizing the regrowth of tumor cells between treatment cycles.

The very first question that arises is why it took 15 years to bring this interesting concept to the clinic. Certainly, the safety of the dose-dense chemotherapy approach was an issue, and it prompted a number of pilot feasibility studies that greatly benefited from the introduction of granulocyte colony-stimulating factors into the clinic. With the use of such growth factors, it became possible to deliver chemotherapy on time, with a low rate of febrile neutropenia. At the same time, much of the energy of the oncology community in the last two decades has been driven by specific drug questions, neglecting most of the other key variables of chemotherapy that might turn out to be of utmost importance, including the timing of chemotherapy in relation to tumor resection and initiation of endocrine therapy, the duration of chemotherapy, and finally, the schedule of drug administration.

WHAT ARE THE STRENGTHS OF INT 9741 BESIDES ITS MATHEMATICAL RATIONALE?

Its design leaves little to criticize: Careful attention has been paid to control all four arms of the trial for the types of agents given (doxorubicin, cyclophosphamide, and paclitaxel) as well as the cumulative doses administered, leaving for analysis solely the variables of interest to the investigators. Possible interactions between chemotherapy and radiation therapy or adjuvant tamoxifen have been eliminated by postponing these other treatment modalities until after the completion of the chemotherapy program. The trial used a 2 × 2 factorial design, which allows us to answer two questions simultaneously, provided that no interaction exists between the treatment arms. The study was adequately powered to detect a 33% difference in hazard for either main effect: disease-free survival or overall survival.

The conduct of the trial was quite satisfactory. Fewer than 2% of the randomized patients did not receive protocol therapy; they were excluded from the analysis, which is not usually done according to the intent-to-treat principle. It is unlikely, however, that the inclusion of these patients would have generated different results. Finally, according to a detailed toxicity analysis on a subset of the trial population, only a small percentage of the patients required dose reduction or dose delay of one or more of their prescribed drugs.

DOES THE CURRENT REPORT OF INT 9741 SUFFER FROM WEAKNESSES?

The answer is yes. The reported data should still be viewed as immature, both in terms of efficacy and safety. Although the results for the first 2 years after randomization are stable, the risk ratio (RR) for both relapse (RR = 0.74; P = .010) and death (RR = 0.69; P = .013) are likely to change as substantially more events are observed during long-term follow-up.

The study was clearly not powered for individual comparisons of the four treatment arms, and such comparisons should be avoided or taken with extreme caution. It is, however, of some concern that the sequential every-3-weeks regimen seems to
perform less well than the current American standard arm of
doxorubicin (A) plus cyclophosphamide (C) followed by pacli-
taxel (T) every 3 weeks (AC → T), raising the possibility that the
therapeutic benefit achieved by switching from this current
standard to either one of the dose-dense regimens might be
smaller than suggested by the $2 \times 2$ main effects analysis.

So far, the toxicity data are rather reassuring: There is no
suggestion of an increased incidence of cardiotoxicity or secondary
leukemia with the dose-dense schedules. However, the definitive
evaluation of the leukemia rate might require additional years of
follow-up, and long-term follow-up in excess of 5 years might be
more suitable for a clear assessment of cardiac risk.

One may regret the lack of quality-of-life evaluation in a
subset of patients enrolled on INT 9741; these data might have
added value to the traditional way of reporting treatment side
effects, strengthened the concept that women in the dose-dense
arms do better overall, and perhaps highlighted subtle differ-
ences between the dose-dense single-agent sequential arm and
the dose-dense combination arm.

Because INT 9741 is a positive trial as far as its first question
is concerned—namely, the superiority of accelerated over con-
ventionally timed chemotherapy—a cost-effectiveness analysis
would also provide useful information to the medical commu-
nity. Although there are obvious concerns about the added cost
of growth factors, a detailed cost/benefit analysis might alleviate
these concerns by balancing higher drug costs against the
reduced costs of toxicity management and loss of productivity.

Perhaps the most relevant criticism of INT 9741 relates to the
lack of prospective stratification for estrogen receptor (ER)
status. Clinical investigations in recent years have drawn our
attention to the fact that the magnitude of the adjuvant chemo-
therapy effect may vary substantially in subgroups of patients
with ER-positive or ER-negative tumors and may be confounded
by its indirect endocrine effects. Two striking examples are the
lack of a significant benefit from AC → T in the ER-positive
subpopulation of Cancer and Leukemia Group B (CALGB) Trial
934412,13 and the extremely poor results of adjuvant cyclophos-
phamide/methotrexate plus fluorouracil (CMF) in very young
women with ER-positive disease who do not experience ovarian
ablation through this treatment modality, in contrast to older
premenopausal women.13 The reported lack of an interaction
between ER status and treatment in INT 9741 does not preclude
the existence of potential confounding variables in the ER-
positive subpopulation, such as a more efficient and more rapid
induction of menopause in young women receiving accelerated
chemotherapy. Half of the women in INT 9741 were younger
than 50 years of age, and two thirds had ER-positive disease. It
will be interesting to see the relapse-free and overall survival
rates relative to the induction of menopause in a more mature
report of this trial.

As we progressively leave the era of empirical medicine and
enter one of molecular medicine, it is becoming increasingly
more obvious that the one-shoe-fits-all theory will find ever
fewer supporters. Recent gene-profiling studies have nicely
confirmed that ER-positive and ER-negative breast cancer are
essentially two different diseases.14,15 Moreover, a further anal-
ysis of the ER-negative subset reveals the existence of at least
two subtypes: an HER-2 overexpressing subset and a basal-like
one. Among the latter, a further subgroup can be delineated with
the overexpression of several key genes involved in cellular
proliferation (Sotiou C, Neo S-Y, McShane L, et al, manuscript
submitted for publication). It is extremely tempting to speculate
that this subset could be the one that derives the greatest benefit
from a chemotherapy dose-densification approach. Unfortu-
nately, INT 9741 has not been adequately powered for subgroup
analyses, and these analyses may be important to better under-
stand how to maximize the clinical utility of chemotherapy in
general and of expensive dose-dense regimens in particular.

DOES INT 9741 STAND ALONE IN A MISTY LANDSCAPE
OF CHEMOTHERAPY DOSE-DENSIFICATION ATTEMPTS?

In the era before taxanes, most investigations of chemotherapy
dose densification for breast cancer treatment generated negative
results, but they have all suffered from severe design limitations.
These include insufficient power, asymmetry between arms with
respect to types of drugs administered, use of suboptimal doses
of drugs, or manipulation of drug density and cumulative doses
at the same time as drug dose, thereby confusing the interpreta-
all the results.16,17 Trials of densified regimens in advanced
breast cancer have been disappointedly small and negative with
regard to progression-free survival and overall survival, although
trends of improved responses have been reported occasionally.

In locally advanced breast cancer, a relatively small trial by the
European Organization for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada/Swiss
Group for Clinical and Epidemiological Cancer Research failed
to show an improvement over the 6-month Canadian cyclo-
phosphamide, epirubicin, and fluorouracil regimen for a
3-month dose-intensified and dose-dense epirubicin-cyclo-
phosphamide (EC) combination given with filgrastim support.
An optimistic view of this trial emphasizes the similar
efficacy of a short course of therapy when compared with a
prolonged one, and with a 5-year follow-up, no increased rate
of cardiotoxicity or acute myeloid leukemia has been ob-
served with the dose-dense strategy.18

In early breast cancer, a small (N = 183) and clearly
underpowered trial targeting a high-risk subset of women with ≥
10 positive nodes or extracapsular invasion showed similar
results for dose-dense EC and conventionally timed EC →
CMF.19 At the same time, a somewhat larger Eastern Coopera-
tive Oncology Group (ECOG) trial (N = 646) showed a trend for
improved disease-free survival with a dose-dense and metron-
omic regimen using continuous oral cyclophosphamide and a
biweekly regimen of doxorubicin, vincristine, and fluorouracil
alternating with biweekly fluorouracil as opposed to standard
American cyclophosphamide, doxorubicin, and fluorouracil.20

The ECOG trial highlights a potential challenge to the
dose-densification concept: Is it possible that chemotherapy
administered at relatively low doses but according to a frequent,
metronomic schedule might be superior to an accelerated,
biweekly schedule? Metronomic chemotherapy is receiving
increasing attention in view of preclinical studies showing that it
optimizes the antiangiogenic effects of cytotoxic agents21-24 and in
view of clear-cut antitumor efficacy in advanced breast cancer.25,26
A metronomic AC regimen given over 15 weeks has been success-
fully piloted by the Southwest Oncology Group (SWOG)27 and will
be soon incorporated into an elegant prospective randomized trial designed to challenge the dose-dense concept.

More provocative data have been generated by dose-densification strategies since taxanes have been introduced. Although we are still anxiously waiting for the results of important trials directly comparing 3-weekly to weekly taxane administration in advanced and early breast cancer, interesting results have been generated in trials of preoperative chemotherapy, suggesting the potential clinical superiority of dose-dense paclitaxel. In an M.D. Anderson Cancer Center trial, the rate of pathologic complete response for patients receiving dose-dense weekly paclitaxel was nearly double that of patients receiving the standard 3-weekly regimen of paclitaxel (25% v 15%; P = .01). This observation raises another important question: Will weekly paclitaxel be as good as or even better than biweekly paclitaxel with granulocyte colony-stimulating factor support? Fortunately, the previously mentioned, innovative SWOG-Intergroup trial comparing the relative merits of dose-dense and metronomic chemotherapy will also address this important question.

Another study from the German group found dose-dense, sequential epirubicin and paclitaxel to be superior to the combination of these agents given according to a standard, 3-weekly schedule. Unfortunately, however, this trial combined both dose-intensity and dose density and did not control for total cumulative doses, which were higher in the dose-dense arm.29

Last among the taxane trials, the reasonably large study (N = 913) by Jackisch et al., recently presented at the San Antonio Breast Cancer Conference, conveys the important message that not all dose-dense regimens will improve patient outcome and that extrapolation of the INT 9741 results to other drugs or combinations is potentially hazardous. In the study by Jackisch et al, a dose-dense doxorubicin-docetaxel regimen given for four cycles was found to be inferior to a more conventional regimen of sequential AC → docetaxel preoperative chemotherapy in terms of complete and pathologically complete responses, as well as in rates of breast conservation.

One interesting trial currently recruiting patients might shed light on the still controversial issue of anthracycline dose-intensity: National Cancer Institute of Canada MA21 compares six cycles of Canadian cyclophosphamide, epirubicin, and fluorouracil with both AC → T (as given in CALGB 9344) and a sequence of dose-dense EC (as given in the previously described locally advanced breast cancer trial coordinated by the EORTC) followed by 3-weekly paclitaxel. The dissociation between dose-dense EC and a conventionally timed taxane might tell us whether there is any merit to accelerated anthracycline/cyclophosphamide administration in a more favorable operable breast cancer population than the one targeted by the EORTC trial.31

It is unclear at this point in time whether dose densification of docetaxel will be of any value, but dose-dense, sequential doxorubicin/docetaxel at full doses has been found to be associated with an excessive rate of severe skin toxicity.32

Collectively, the current data indicate that the superiority of a sequential dose-dense approach might be specific to paclitaxel; the data on docetaxel are too scarce and suboptimal in nature, and the data on anthracyclines are not convincing.

**SEQUENTIAL SINGLE AGENTS OR COMBINATION THERAPY?**

The second question posed by INT 9741—namely, the potential superiority of sequential single agents over their combined use—has received a negative answer thus far. This does not mean that the concept is wrong: INT 9741 is by today’s standards a relatively small trial, and it may have missed a small, but still significant, clinical benefit. It is quite likely that ongoing or recently closed adjuvant trials of the taxane era will be able to provide a definitive answer to this question after a meta-analysis. Indeed, close to 10,000 women have been enrolled onto such trials, highlighting the strong interest of oncologists in this question.33 Furthermore, the fact that the sequential regimens seem to yield a similar efficacy with a more favorable toxicity profile is also an important message to retain from INT 9741. It should, however, be noted that in the pretaxane era, SWOG 0137 failed to show the expected 30% increase in disease-free survival with sequential, increased doses of doxorubicin/cyclophosphamide over their combined administration, and the sequential treatment course was more toxic.34 In the taxane era and in advanced disease, an ECOG trial showed similar survival for sequential paclitaxel/doxorubicin (or the reverse sequence) and for the combined use of the drugs.35

**WHAT ARE THE IMPORTANT MESSAGES FROM INT 9741 FOR THE ONCOLOGY COMMUNITY?**

For oncologists involved in clinical research, the message is that choice of which chemotherapy drugs to use is not the only way forward: The schedule of drug administration is an important variable, in addition to the timing and duration of chemotherapy, which might also play a role but have been poorly investigated to date. Now it is our task to confirm these data independently with a much larger trial that will allow identification of subgroups that derive substantial benefit from the dose-densification approach.

On the basis of a single trial of 2,000 women, it would not be wise for clinicians in practice to routinely adopt accelerated chemotherapy for all patients with high-risk breast cancer. Nevertheless, while waiting for the confirmatory evidence, the individualized use of these dose-dense regimens as given in INT 9741 for high-risk women—particularly for those who cannot count on beneficial effects of adjuvant endocrine therapy—is not unreasonable, provided that the women are informed about the uncertainties regarding the risk/benefit ratio of dose-dense therapies. A last, but certainly no less important, message is that it might be dangerous and harmful to extrapolate the results of INT 9741 to other drugs or combinations.

Overall, Citron and his colleagues must be congratulated for what could well be a landmark adjuvant trial in breast cancer. This study symbolizes the marriage between mathematics and breast cancer chemotherapy after a 15-year romance. The future will tell us if this is a life-long relationship.

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Mathematics and oncology: a match for life?  J Clin Oncol. 2003 Apr 15;21(8):1425-8. doi: 10.1200/JCO.2003.12.068. To participate, choose one subject, mathematics or computer science, a university and the programme you want to study in Russia. Do not forget to carefully read the requirements of the organizers on the Olympiad website. After registering, you will receive access to a training session and be able to study the problems of past competitions and immerse yourself in the specifics of the contest. The Olympiads have two main stages: the online qualifying stage will be held from December 5 to March 10, and the finals are set on March 23, 2021, to attend in person or remotely. The research group "Mathematics in Life Sciences" is working on mathematical and computational methods for molecular systems biology. The main focus is on constraint-based and optimisation-based approaches for analysing the structure and dynamics of metabolic and regulatory networks. The mathematical background of the group lies in discrete mathematics and optimisation, constraint/integer programming, and computational logic. For more information, please visit the Research and Projects section. A computational model of phototrophic growth of the cyanobacterium Synechococcus elongatus A level Pure Mathematics 2 & 3. Offers help for the syllabus as a feature of an arrangement of assets. This reading material gives full scope of Pure Mathematics 2 and 3 (P2 and 3). Fully endorsed by OCR and revised to match the 2005 specification, this series has been carefully revised by experienced teachers and provides easy to use texts. Cambridge Advanced Mathematics for OCR encourages achievement by supporting revision and consolidation through review exercises and mock exam papers written by experienced examiners. The content incorporates exercises, examinations for A level Mathematics and reviewed activities to give a lot of training. Additional data and test material for this asset. Download A level mathematics statistics 2 pdf here: Download. Ramanujan Mathematical Society Little Mathematical Treasures INMO IMO Math Olympiad A Gateway to M Mathematical Problems and Puzzles from the Polish Mathematical Olympiads. 379 Pages·2010·20.96 MB·42,799 Downloads. Mathematical Olympiad in China. 1985. In commemorating him, a competition named Hua Luogeng. Gold Singapore Mathematical Olympiad Training Handbook - Sec 1.